cell lines and clinical samples, a deletion in 6q21 was most frequent.[7] Several candidate genes were found in a minimal common region (MCR) in 6q21 but no functional studies were conducted to confirm a tumor suppressor role.[7,8] Karube et al performed several key experiments to support their hypothesis that *PRDM1* and forkhead transcription factors of the O class (*FOXO3*) are tumor suppressor gene candidates implicated in pathogenesis of ENKTL and ANKL.[1] First, they tested a relatively large number of clinical samples and cell lines, identifying 7 gene candidates in 2 MCRs in 6q21 chromosome. Second, they created a novel elegant experimental model to study the functional role of each gene. The re-expression of only 2 genes, *FOXO3* and *PRDM1*, resulted in the inhibition of the pro-liferation of experimental NK cells. Third, they validated the results from the gene ex-pression profiling and confirmed that FOXO3 and PRDM1 were down-regulated in a major-ity of the clinical samples and cell lines includ-ing the samples with the absence of del(6q21). Fourth, they discovered several nonsense mu-tations in *PRDM1* and missense mutations in *FOXO3*, which is consistent with "2-hit" hy-pothesis. While the jury is still out on the role of other deleted genes in chromosome 6q21 in the pathogenesis of NK-cell malignancies, the implications from this report can be far-reaching

FOXO3 is a member of the FoxO family of transcription factors regulating numerous cellular processes.[10] This factor has not been extensively studied in human lymphomas, but a recent study identified *FOXO3* in the most frequently deleted MCR in chromosome 6q21 in several types of B-cell lymphoproliferative disorders.[11] In experimental animal studies, somatic deletions of all alleles of 3 *FOXO* members resulted in the development of pro-gressive thymic T-cell lymphomas and hem-angiomas.[12] Because both FOXO3 and PRDM1 are transcription factors integrated in multiple intracellular signal transduction pathways, an understanding of the deregula-tion of these pathways in NK-cell lymphoma will be important for the identification of therapeutic targets and the development of effective treatment strategies.

However, as is common for any novel find-ing, many questions arise from this work. Is the down-regulation of FOXO3 and PRDM1 a primary or secondary event in lympho-magenesis? Is the inactivation or down-regulation of both tumor suppressors neces-sary for the development of the disease phenotype? What are the most frequent mechanisms responsible for down-regulation of FOXO3 and PRDM1 in patients with EN-KTL and ANKTL without del(6q21)? What is the role of EBV in the pathogenesis of NK lymphomas and how it interacts with FOXO3 and PRDM1? In summary, there is no doubt that the work of Karube and colleagues is an important step forward in our understanding of the molecular pathogenesis of ENKTL and ANKL, which could open the door for excit-ing new research.

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● ● ● **TRANSPLANTATION**

Comment on Robb et al, page 3399

Type I-IFNs interfere with GVH responses

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Just as type I-IFNs interfere with viral replication and autoimmunity, Robb et al report that they can also interfere with GVHD and GVL responses after allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1,2]

Following allo-HSCT, donor T cells react with either HLA-mismatched or -matched but genetically distinct host, provid-ing a beneficial GVL response but also result-ing in harmful GVHD. The development of GVHD thus represents a major obstacle to successfully harnessing the curative potential of GVL. Robb and colleagues report that care-fully calibrated use of type I-IFN impairs the bad GVHD and restores the good GVL after allo-HSCT.[1,3]

The early chordates that developed in the adaptive immune system also developed the type I-IFN cytokine family. They were dis-covered by Isaacs and Lindenmann and named interferon because of their ability to interfere with in vitro viral replication.[2] Type I-IFNs constitute multiple cytokines, although from an immunologic perspective, the most relevant are the IFN-α subsets and IFN-β.[2] They rep-resent a key link between the innate and adap-tive immune responses.[2] The relevance of en-dogenous type I-IFN in human immunology is demonstrated by enhanced susceptibility to viral (HSV) infections in patients with inborn errors in type I-IFN–mediated immunity.[4] The effects of exogenous type I-IFNs are well-documented by the clinical application of IFN-α in viral infections, renal carcinoma, and melanoma and IFN-β in multiple sclero-sis.[2,5] IFN-α and -β share a ubiquitously ex-pressed heterodimeric receptor composed of

IFNAR1 and IFNAR2 subunits that signal through the Jak-STAT1 pathways and induce several genes that contain the IFN-stimulated response elements and γ-activated sequences.[2,4]

The role of type II-IFN, IFN-γ, and several other cytokines has been well studied in the context of GVH responses.[3] Despite being the earliest discovered members of the cytokine family, the role of type I-IFNs and their ability to interpose the processes of GVHD and GVL has been largely unexplored until now. In this issue, Robb and colleagues report that IFNAR1 signaling in the host mitigates GVHD mortality and GI tract (colonic) pathology, reduces alloreactive donor T-cell expansion, and decreases cytopathic Th1 and Th17 cytokines in major histocompatibility complex (MHC) mismatched, CD4+ T-cell dependent models of GVHD.[1] The authors also demonstrate that deficiency of type I-IFN signaling in the host hematopoietic cell compartment is critical for this impact on GVHD. They posit that this is independent of the effect on donor regulatory T cells (Tregs) but is partially dependent on generation of donor Th17 cells. Notably, the authors demonstrate that a single-injection IFN-α on day −1 reduced expansion of donor T cells and Th1 and Th17 cytokines exclusively in the wild-type animals but not in the IFNAR1−/− animals. By contrast, paradoxically CD8+-mediated GVHD was reduced in the absence of type I-IFN signaling in host tissues after MHC class I mismatched and MHC matched but minor disparate allo-HSCT. This was because of differential resistance of host tissues to donor CD8+-mediated cytolysis but not because of direct impact on the CD8+ T-cell intrinsic cytotoxic effects. Thus, intact signaling through IFNAR1 in the host mitigates CD4+-mediated but enhances CD8+-mediated GVHD.[1]

T cells exhibit exquisite response to type I-IFN.[2,5] What impact would donor T-cell responses to type I-IFN have on GVHD? Using donor allografts from IFNAR1−/− donors, the authors show that donor IFN signaling on donor T cells did not alter mortality from GVHD. Importantly, administration of type I-IFN, namely IFN-α, after bone marrow transplantation (BMT) promoted better tumor clearance (GVL) when the tumors also expressed IFNAR1.[1]

These observations appear to be in contrast to previous observations demonstrating only mild impact on CD8+-mediated hepatic GVHD and lack of impact on alloreactivity in CD8+-mediated skin allograft rejection model.[6,7] The milder nature of GVHD in the model systems, the differences in T-cell doses, and intensity of inflammation might explain the divergent results. Nonetheless, the observations from this study by Robb et al help clarify the clinical observation of increased GVHD severity when IFN-α was administered early after BMT.[8]

Like all interesting studies, this one, while illuminating the role of type I-IFNs in GVHD and GVL, also raises additional questions. What are the main inducers and primary cellular sources of type I-IFNs after BMT? Why the specificity for GI target (colon)? What is the key cellular target for IFN-α in the host compartment? How and why does type I-IFN signaling modulate target tissue resistance only to CD8+ T-cell cytolysis? What is the effect of type I-IFN signaling on other donor cellular subsets that affect GVHD and GVL, namely donor natural killer cells, plasmacytoid DCs, and Tregs (where STAT-1 signaling has recently been shown to be critical)?[9] Is there an effect on overall functional immune-competence? What is the effect on CD4+-mediated GVL? This study thus provides novel insights on the role of type I-IFN in allo-HSCT and

provides texture to our current understanding of the role of cytokines in GVHD and GVL. Importantly, in light of the availability and known clinical effects of type I-IFNs, the observations of Robb and colleagues suggest that IFN-α can be harnessed for enhancing clinical GVL responses. The administration of IFNα (or its pegylated forms) might therefore be considered as an adjunct to standard therapy in carefully designed clinical trials to augment GVL for high-risk hematologic malignancies after clinical allogeneic HSCT.

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